related complexes, which could reveal novel, interesting features due to their increased electrophilicity and coordinative unsaturation with respect to the cationic metallocenes.

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Supplementary Material Available: Listings of ^1H and ^{13}C NMR data for **1** and **2**, a summary of X-ray data, tables of positional and thermal parameters and bond distances and angles, and a crystal packing diagram for **1**·$PhCH_3$ (7 pages). Ordering information is given on any current masthead page.

Ellagitannin Chemistry. The First Example of Biomimetic Diastereoselective Oxidative Coupling of a Glucose-Derived Digalloyl Substrate

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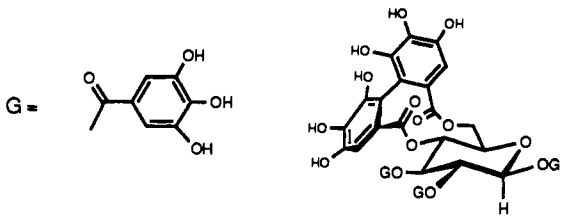
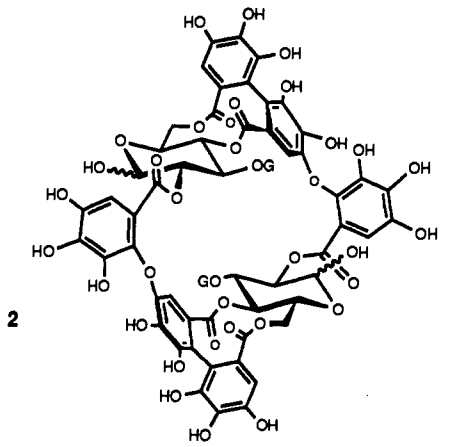
Ellagitannin natural products comprise an extensive group of structurally characterized secondary plant metabolites whose myriad subclasses result from expression of almost all the possible modes of oxidative coupling of appropriately juxtaposed galloyl groups attached to a glucose core. Thus, the monomeric ellagitannin tellimagrandin II (**1**)[2] contains a 4,6 coupled (*S*)-hexahydroxydiphenyl (HHPD) unit, while the dimeric congener oenothein B (**2**)[3] not only has this same HHDP moiety but also displays a second C–O coupling within the valoneoyl ester linking bridge. In addition, other members of this class of natural products feature C–C coupling between galloyl groups at the 2,4,[4] 3,6,[4a-c,5] and 1,6[4c] positions of the glucose ring, as well as C–O coupling (in dimeric ellagitannins) between 1,1′, 1,2′, 1,6′, 2,4′, 2,6′, and 3,4′ galloyl residues.[1c] Schmidt[1a] and later Haslam[1b,d] have postulated that the stereochemical and regiochemical outcome of the oxidative coupling processes of glucose-bound galloyl units is a direct and predictable consequence of the conformational preferences of the precursor molecules. In the results described below, we report the *first examples of high-yielding, completely diastereoselective (atrop-selective) coupling of galloyl species at the 4 and 6 positions of a glucose derivative using $Pb(OAc)_4$ as the oxidant.*[6] These experiments provide the *first support for the Haslam/Schmidt hypothesis*, as the conformational preferences of the digallate substrate (vide infra) are translated faithfully to the naturally occurring ellagitannin stereochemistry upon oxidation.



1



2

Historically, the defining attribute of gallotannins that has prompted much experimental inquiry is their ability to recognize and bind to almost all proteins examined.[1b] Manifestations of this phenomenon can be found, inter alia, in leather tanning, wine aging, and the salubrious properties of herbal teas. In addition to the generalized surface interactions between proteins and gallotannins which presumably underlie these applications,[1b] recent studies have documented that several of the more structurally complex ellagitannins engage in what is likely a very specific interaction with various disease-associated target enzymes, thus highlighting their therapeutic potential.[7] Despite their appealing structural complexity and potential as tools to study protein/ligand interactions, no investigations into the synthesis of the ellagitannins have been reported. Furthermore, even simple galloyl esters (and gallic acid) have continually defied attempts at oxidative phenolic coupling, instead providing modest yields of ellagic acid in most cases.[8]

We have initiated a program of synthesis whose goals include the development of diastereoselective oxidative phenolic coupling protocols to provide the various (*S*)- or (*R*)-HHDP units mentioned above. Toward this end, we have screened several di-, tetra-, and hexamethylated analogs of the digalloyl glucose-derived substrate **3** with a range of reagents reputed to be useful for oxidative phenolic coupling. One successful combination featured

(1) Leading references can be found in the following reviews: (a) Schmidt, O. T. *Fortschr. Chem. Org. Naturst.* **1956**, *13*, 70. (b) Haslam, E. *Plant Polyphenols*; Cambridge University Press: Cambridge, 1989. (c) Okuda, T.; Yoshida, T.; Hatano, T. *Heterocycles* **1990**, *30*, 1195. (d) Gupta, R. K.; Al-Shafi, S. M. K.; Layden, K.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2525.

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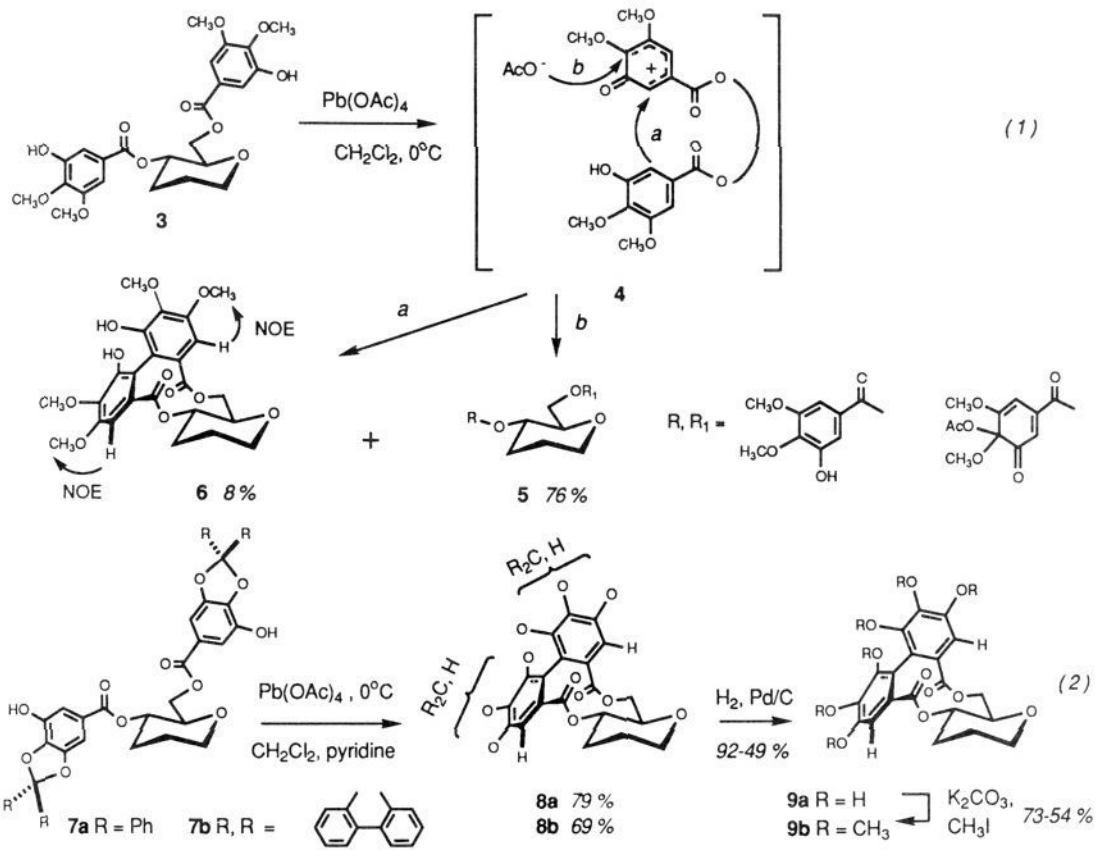
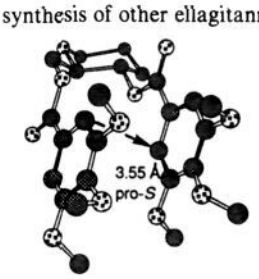
Chart I



$Pb(OAc)_4$ and the particular bis dimethylgalloyl candidate **3**:[9] reaction of **3** with $Pb(OAc)_4$ in CH_2Cl_2 at 0 °C afforded small amounts of the (*S*)-HHDP-containing product **6**[9b] along with a mixture of the stable monoquinone ketals **5** in good yield, eq 1 (Chart I). Despite the low yield, it is notable that the biphenyl species **6** was formed with complete stereo-[10a] and regiochemical[10b] control. We speculate that a common electrophilic intermediate, whose reactivity presumably resembles that of the cation **4**, precedes both compounds, and that the ratio of products reflects the competition for this species by the inter- and intramolecular nucleophiles present (eq 1).

Guided by this mechanistic hypothesis, the more sterically encumbered (with respect to path b but not path a) diphenyl and fluorenyl ketals, **7a** and **7b**, respectively,[9b] were prepared and subjected to $Pb(OAc)_4$-mediated oxidation in an effort to influence the partitioning of the putative cyclohexadienyl cation **4**. We were delighted to find that formation of HHDP-containing species **8a**/**b** had occurred to the complete exclusion of quinone ketal, eq 2! In these instances, all four possible regioisomers of HHDP-containing products **8a** (2.0:1.6:1.5:1.0 ratio) and three of the four regioisomers of **8b** (1.6:1.3:1.0 ratio) were isolated following silica gel chromatography. Subsequent conversion of each regioisomer, independently, to the same stereoisomer of the permethylated species **9b**[9b,10a] demonstrated that the high level of diastereoselectivity observed in eq 1 had not been compromised. From the standpoint of ellagitannin synthesis, this lack of regioselectivity is of no consequence.

In summary, the $Pb(OAc)_4$-mediated oxidative phenolic coupling of a suitably protected digalloyl glucose derivative proceeds with complete diastereoselectivity to afford the naturally occurring (*S*)-HHDP unit. The stereochemical outcome of this process is in complete accord with the Haslam/Schmidt ellagitannin biosynthesis hypothesis. That the glucose-derived template **3** aligns the aromatic residues in an appropriate position for diastereoselective coupling is suggested by the results of molecular mechanics[11] calculations. Thus, the "global minimum" conformation of the hexamethyl ether corresponding to **3** juxtaposes those carbons destined to unite just 3.55 Å apart (cf. **10**), while other possible pairings from this conformation are displaced considerably further apart. In any event, studies designed to probe the utility of this biomimetic oxidative cyclization methodology for the synthesis of other ellagitannin coupling patterns are in progress.



10 *hydrogens ommitted for clarity*

Acknowledgment. We thank the NIH for financial support.

Supplementary Material Available: Experimental procedures and spectral data (^1H NMR, ^{13}C NMR, IR, LRMS, HRMS, CD where appropriate) for **3**, **5**, **6**, **7a**/**b**, **8a**/**b**, and **9a**/**b** (9 pages). Ordering information is given on any current masthead page.

(9) (a) Commercially available D-glucal triacetate was converted to the diol corresponding to **3** via a known procedure (Lemieux, R. U.; Brewer, J. T. *Adv. Chem. Ser.* **1973**, *117*, 121). This diol was acylated (DMAP, DMAP·HCl, DCC) with 3-*O*-benzyl-4,5-di-*O*-methylgallic acid (78%), and the benzyl groups were removed by hydrogenolysis (Pd/C, H_2, 100%) to afford **3**. (b) Experimental procedures and full spectral data are available in the supplementary material.

(10) (a) The stereochemistries of diol **6** and hexaether **9b** were ascertained by CD analysis, wherein a positive Cotton effect at 230 nm was observed. CD has been used numerous times to unambiguously identify the absolute stereochemistry of HHDP units in both naturally occurring ellagitannins and their per-*O*-methyl derivatives. See: Okuda, T.; Yoshida, T.; Hatano, T. *J. Nat. Prod.* **1989**, *52*, 1. (b) The regiochemistry of coupling in **6** was determined by DNOE measurements as indicated.

(11) Molecular mechanics calculations were performed with Macromodel 3.1x using a directed Monte Carlo search of conformational space about all rotatable bonds (1000 starting conformations).